PATENT SPECIFICATION

798,655

Inventors:—SIEGFRIED GOTTFRIED and LILY BAXENDALE.

Date of filing Complete Specification: *March 12, 1957.*

Application Date: *March 15, 1956.* No. 8183/56.

PATENTS ACT, 1949

SPECIFICATION NO. 798,655

In accordance with the Decision of the Superintending Examiner, acting for the Comptroller-General, dated the twenty third day of January, 1961, this Specification has been amended under Section 14 in the following manner:-

Page 1, lines 19/20, *delete* "functional derivatives" *insert* "salts and esters"

Page 1, line 21, *after* "name." *insert* "It is to be understood that where an ester or salt of glycyrrhetinic acid is used, the compound used to form said salt or ester is non-toxic

Page 2, line 44, *after* "have" *for* "shown" *read* "suggested".

Page 2, line 45, *after* "acid" *delete* "has pharmacological" *insert* "may have".

Page 3, *delete* lines 14 to 18 inclusive.

Page 3, line 19, *for* "EXAMPLE 7" *read* "EXAMPLE 3"

Page 3, line 25, *for* "EXAMPLE 8" *read* "EXAMPLE 7"

THE PATENT OFFICE,
25th February, 1961.

DS 97412/1(2)/B.153 200 2/61 PL

organisms or by chemical irritants, or allergens, or parasites, or fungi-, or where there is an organic disfunction, a condition of inflammation develops which may be severe enough to cause the breakdown of cells. Many therapeutic agents in the form of ointments, lotions, dusting powders have been used for the treatment of such conditions and these normally depend for their action on combating the primary offensive agent, that is to say an antibiotic, antiseptic, bactericidal, chemotherapeutic or bacteriostatic substance is used where the disease is of microbial origin or a fungicidal or insecticidal substance is used where the disease is of fungus or parasitic origin or an antihistaminic substance is used where the disease is due to the release of histamines or other allergens. Barrier creams are used prophylactically where physical or chemical agents are likely to cause skin disorders.

[illegible]

or more anti-causative substances which are antibiotic, antiseptic, bactericidal, bacteriostatic, fungicidal, insecticidal or antihistaminic substances and optionally an anti-inflammatory substance, such as a corticosteroid, a Vitamin B compound or analogue, in admixture with glycyrrhetinic acid or a salt or ester thereof, conveniently in the form of an admixture with an inert carrier base comprising an emulsion, lotion, ointment (including a barrier cream) or powder.

By the use of the compositions of the present invention there is achieved an enhanced therapeutic effect since the correction of the inflammation by the glycyrrhetinic acid or its derivative proceeds simultaneously and synergistically with the combating of the causative agent of such inflammatory process by the anti-causative substance and thus brings about a more rapid return of the tissues to their normal state and hence a

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Index at Acceptance :—Class 81(1), B1(D : R : S : Z).

International Classification :—A61k.

COMPLETE SPECIFICATION.

Improvements in or relating to Therapeutic Compositions.

We, BIOREX LABORATORIES LIMITED, a British Company, of 47/51 Exmouth Street (Mkt.), Rosebery Avenue, London, E.C.1, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to improved therapeutic preparations containing Liquorice root (Glycyrrhiza) derivatives for topical application.

The Liquorice root derivatives with which the present invention is concerned are those compounds obtainable from an extract of liquorice which exhibit an anti-inflammatory activity similar to that of cortisone and hydrocortisone and which are generally known as glycyrrhetinic acid and its functional derivatives and are hereinafter referred to by that name.

Where the skin is attacked by micro-organisms or by chemical irritants, or allergens, or parasites, or fungi-, or where there is an organic disfunction, a condition of inflammation develops which may be severe enough to cause the breakdown of cells. Many therapeutic agents in the form of ointments, lotions, dusting powders have been used for the treatment of such conditions and these normally depend for their action on combating the primary offensive agent, that is to say an antibiotic, antiseptic, bactericidal, chemotherapeutic or bacteriostatic substance is used where the disease is of microbial origin or a fungicidal or insecticidal substance is used where the disease is of fungus or parasitic origin or an antihistaminic substance is used where the disease is due to the release of histamines or other allergens. Barrier creams are used prophylactically where physical or chemical agents are likely to cause skin disorders.

None of the substances or classes of substances mentioned above has specifically anti-inflammatory properties and their use does not in itself reduce the inflammation. Indeed, in some cases, the anti-bacterial agents such as, say penicillin or certain quaternary ammonium salts, are themselves known in many cases to give rise to an inflammatory condition and, even if the causative agent, e.g. the bacteria or fungus, has been destroyed, the inflamed condition may persist for some time.

An object of this invention is to provide a means of increasing the efficiency of such preparations. An anti-inflammatory agent will, of course, reduce initially inflammation but, of itself, has no effect on the primary causative agent and frequency assists the spread of an infection by inhibiting normal tissue reaction.

According to the present invention, there is provided a composition comprising one or more anti-causative substances which are antibiotic, antiseptic, bactericidal, bacteriostatic, fungicidal, insecticidal or antihistaminic substances and optionally an anti-inflammatory substance, such as a corticosteroid, a Vitamin B compound or analogue, in admixture with glycyrrhetinic acid or a salt or ester thereof, conveniently in the form of an admixture with an inert carrier base comprising an emulsion, lotion, ointment (including a barrier cream) or powder.

By the use of the compositions of the present invention there is achieved an enhanced therapeutic effect since the correction of the inflammation by the glycyrrhetinic acid or its derivative proceeds simultaneously and synergistically with the combating of the causative agent of such inflammatory process by the anti-causative substance and thus brings about a more rapid return of the tissues to their normal state and hence a

reduction in the damage thereto, such results being unobtainable in the same time, and with such little discomfort to the patient, if the glycyrrhetinic compound and the anti-causative substance are used independently.

Among the anti-causative substances may be mentioned the various sulphonamide compounds, bactitracin, cetrimide, penicillin, chlortetracycline, tetracycline, Neomycin, hexyl resorcinol, the flavines and diaminodiphenylsulphone, which are examples of antibiotic, and bactericidal compounds; chlorinated phenols, which are antiseptic compounds; chlorocresol and chloroxylenol which are bacteriostatic compounds; zinc undecylenate and phenylmercuric acetate which are fungicidal compounds; hexachlorobenzene and dichlorodiphenyl-trichloroethylene which are insecticides; and mepyramine salts, such as the maleate, which are antihistamines.

Certain pharmacological properties of glycyrrhetinic acid have been mentioned by F.E. Revers (Ned. Tijdschr. Geneesk. Vol. 92, P. 2968, 1948) who observed that liquorice juice caused water retention; J. A. Molhuysen, J. Gerbrandy, L. A. de Vries, J. C. de Jong, J. B. Lenstra, K. P. Turner and J. G. G. Borst (The Lancet, Vol. 2, P. 381, 1950) who reported changes in the potassium balance brought about by the administration of the juice, and R. J. Calvert (The Lancet, Vol. 1, P. 805, 1954) who reported having maintained a patient with Addison's disease on liquorice extract for a year. F. D. Hart and J. C. Leonard (The Lancet, Vol. 1, P. 804, 1954) found some evidence that glycyrrhetinic acid potentiated the action of cortisone; E. E. Galal (British Journal of Pharmacology, Vol. 10, P. 305, 1955) showed that it caused water retention in the tissues and in the gut, and A. C. Adamson and W. G. Tillman (British Medical Journal, P. 1501, 1955) have shown that glycyrrhetinic acid has pharmacological actions resembling those of hydrocortisone.

We have found that the conjoint use of the glycyrrhetinic acid substance with the anti-causative substance results in increased effectiveness of the above clases of substance so as to provide a truly synergistic effect, that is to say there is obtained a therapeutic effect so enhanced and accelerated beyond what may be expected of either constituent alone or if they were used separately, as to constitute synergism.

We have found that glycyrrhetinic acid, its salts or its esters (although not antiseptic in their action) when applied alone to inflamed skin have anti-inflammatory properties and we have demonstrated their activity in such human skin diseases as Pruriginous Dermatoses, Pruritus Ani, Pruritus Vulvae, Topic and Atopic Dermatitis, Erythematous skin conditions, Infantile and Adult Eczemas, contact Dermatitis, Industrial Dermatitis, Nummular Eczema, Acute and Chronic Dermatitis, Allergic Skin Conditions, Seborrhoeic Dermatitis, Dysidrotic Eczema, Psoriasis, Pruritus of Pre-mycosis fungoides type and other inflammatory and pruriginous skin conditions.

The compositions of the present invention also allay inflammation and Pruritus of the small animals and birds, such as dogs and cats, e.g. Dermatitis, Acute Moist Eczema (Wet Eczema), Acanthosis Nigricans, Miliary Eczema (of cats), Pruritus, particularly localised Pruritus, e.g. Traumatic Pruritus of the axilla in short-legged dogs (dachshunds), Dermatitis, such as Sweet Itch (Summer Itch) in horses. Other conditions, such as Otitis Externa, Otitis Media, of dogs, cats and other small animals, Conjunctivitis, Keratitis, varying dermatoses in small and large animals as well as in birds, all inflammatory skin conditions associated with bacteria, and parasites, infections in animals, such as Mange (pigs, cattle, horses and dogs), e.g. Urticarial Irritation in cattle, and Mastitis, both acute and chronic; the incorporation of an enzyme, e.g. trypsin, papain, will jointly assist the elimination of tissue debris.

Glycyrrhetinic acid and its salts and esters also have a marked effect on tissue granulation and act as a healing decongestant.

The following Examples will serve to illustrate the present invention but without limiting its scope, the percentage Figures quoted being calculated by weight:

EXAMPLE 1.

An ointment was prepared by dispersing 2% of glycyrrhetinic acid and 0.5% of Neomycin sulphate in a base of Vaseline (Registered Trade Mark) petroleum hydrocarbons. This ointment completely cured a resistant case of impetigo contagiosa in seven days after complete failure had been experienced on treatment with a Neomycin sulphate ointment similar to the above but omitting the glycyrrhetinic acid.

EXAMPLE 2.

An ointment was prepared by dispersing 2% of glycyrrhetinic acid, 0.5% of cetrimide, 8% of non-ionic emulsifying wax "Lanbritol" (Registered Trade Mark) and 16% of liquid paraffin in water.

EXAMPLE 3.

An emulsion was prepared by dispersing 0.5% of glycyrrhetinic acid, 0.5% of hexachlorophene, 5% of "Lanbritol" 30% of glycerine and 20% of ethyl alcohol in water.

EXAMPLE 4.

A lotion was prepared by suspending 2% of glycyrrhetinic acid, 1% of colourless coal

tar fractions (containing cresylic acid) and 10% of polyethylene glycol (molecular weight 400) in water.

EXAMPLE 5.

A lotion was prepared by suspending 1% of glycyrrhetinic acid, 0.5% of hydrocortison, 0.5% of the coal tar fractions of Example 4 and 10% of polyethylene glycol (molecular weight 600) in water. This example illustrates the substitution of part of the hydrocortisone in a known preparation by glycyrrhetinic acid with enhanced anti-inflammatory effect.

EXAMPLE 6.

A suppository was prepared by dispersing 1.285% of glycyrrhetinic acid and 2.57% of benzocaine in a suppository base (British Pharmaceutical Codex).

EXAMPLE 7.

A dusting powder was prepared by intimately admixing 2% of glycyrrhetinic acid and 0.1% of 2-(benzhydryloxy)-N:N-dimethylethylamine hydrochloride in lactosum.

EXAMPLE 8.

Pellets for use in dental sockets were prepared by dissolving 1% of glycyrrhetinic acid, 2% of cinchocaine (an analgesic) and 0.5% Neomycin sulphate in ethyl alcohol and impregnating cotton wool with the solution.

WHAT WE CLAIM IS:—

1. A synergistic composition for topical application comprising one or more anti-causative substances as hereinbefore defined and optionally an anti-inflammatory substance in admixture with glycyrrhetinic acid or a salt or ester thereof.
2. A synergistic composition according to Claim 1, wherein said composition is dispersed in an inert carrier base.
3. A synergistic composition according to Claim 2, wherein said carrier base is an ointment, emulsion or aqueous solution.
4. A synergistic composition according to Claim 2, wherein said carrier base is a dusting powder composition.
5. A synergistic composition for topical application substantially as described in any of the Examples.

CARPMAELS & RANSFORD,
Chartered Patent Agents.

PROVISIONAL SPECIFICATION.

Improvements in or relating to Therapeutic Compositions.

We, BIOREX LABORATORIES LIMITED, a British Company, of 47/51 Exmouth Street (Mkt.), Rosebery Avenue, London, E.C.1, do hereby declare this invention to be described in the following statement:—

This invention relates to improved therapeutic preparations containing glycyrrhetinic acid for topical application.

Where the skin is attacked by micro-organisms or by chemical irritants, or allergens, or parasites, or fungi, or where there is an organic disfunction, a condition of inflammation develops which may be severe enough to cause the breakdown of cells. Many therapeutic agents in the form of ointments, lotions, dusting powders have been used for the treatment of such conditions and these normally depend for their action on combating the primary offensive agent, that is to say an antibiotic, antiseptic, bactericidal, chemotherapeutic or bacteriostatic substance is used where the disease is of microbial origin or a fungicidal or insecticidal substance is used where the disease is of fungus or parasitic origin or an antihistaminic substance is used where the disease is due to the release of histamines or other allergens. Barrier creams are used prophylactically where physical or chemical agents are likely to cause skin disorders.

None of the substances or classes of substances mentioned above has specifically anti-inflammatory properties and their use does not in itself reduce the inflammation. Indeed, in some cases, the anti-bacterial agents such as, say pencillin, or certain quaternary ammonium salts, are themselves known in many cases to give rise to an inflammatory condition and even if the causative agent has been destroyed, the inflamed condition may persist for some time.

An object of this invention is to provide a means of increasing the efficiency of such preparations. An anti-inflammatory agent will, of course, reduce initially inflammation but of itself has no effect on the primary offensive agent and frequently assists the spread of an infection by inhibiting normal tissue reaction.

According to the present invention there is provided a composition comprising an antibiotic, antiseptic, bactericidal, chemotherapeutic, bacteriostatic, fungicidal, insecticidal or antihistaminic substance, a Vitamin B compound or analogue, or a mixture of said anti-causative substances, in admixture with glycyrrhetinic acid or a

functional derivative thereof, conveniently in the form of an admixture with a carrier base comprising an emulsion, lotion, ointment (including a barrier cream) or powder.

By the use of the compositions of the present invention there is achieved an enhanced therapeutic effect since the correction of the inflammation by the glycyrrhetinic acid or its derivative proceeds simultaneously with the combating of the causative agent of such inflammatory process by the anti-causative substance and thus brings about a more rapid return of the tissues to their normal state and hence a reduction in the damage thereto, such results being unobtainable in the same time and with such little discomfort to the patient if the glycyrrhetinic compound and the anti-causative substance are used independently.

Among the antibiotic substances may be mentioned the various sulphonamide compounds, cetrimide, penicillin, chlortetracycline, tetracycline and diaminodiphenylsulphone.

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It will be realized from the foregoing that the compositions of the present invention are of great value in the treatment of inflammatory conditions in both human and veterinary medicine.

CARPMAELS & RANSFORD,
Chartered Patent Agents,
and
Agents for the Applicants.

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